

What is claimed is:

1. A substantially pure Mcl-1 gene regulatory element, comprising a sequence of at least about twenty contiguous nucleotides of a nucleotide sequence set forth as  
5 nucleotides 1495 to 1657 of SEQ ID NO: 1.

2. The Mcl-1 gene regulatory element of claim 1, comprising nucleotides 1513 to 1564 of SEQ ID NO: 1.

10 3. The Mcl-1 gene regulatory element of claim 1, comprising a nucleotide sequence selected from the group consisting of:

nucleotides 1495 to 1550 of SEQ ID NO: 1;

nucleotides 1495 to 1564 of SEQ ID NO: 1;

nucleotides 1495 to 1606 of SEQ ID NO: 1;

15 nucleotides 1513 to 1550 of SEQ ID NO: 1;

nucleotides 1513 to 1564 of SEQ ID NO: 1; and

nucleotides 1513 to 1606 of SEQ ID NO: 1.

4. The Mcl-1 gene regulatory element of claim 1, comprising a nucleotide  
20 sequence selected from the group consisting of:

nucleotides 1550 to 1657 of SEQ ID NO: 1; and

nucleotides 1606 to 1657 of SEQ ID NO: 1.

5. The Mcl-1 gene regulatory element of claim 1, comprising  
25 nucleotides 1495 to 1657 of SEQ ID NO: 1.

6. A vector, comprising the Mcl-1 gene regulatory element of claim 1.

7. The vector of claim 6, which is an expression vector.

30 8. The vector of claim 6, further comprising a heterologous nucleic acid molecule operatively linked to said Mcl-1 gene regulatory element.

9. A host cell containing the vector of claim 6.

5 ~~10.~~ A substantially pure nucleic acid molecule encoding an Mcl-1 polypeptide, the nucleic acid molecule comprising nucleotides 1727 to 3884 or SEQ ID NO: 1; or a nucleic acid molecule complementary thereto.

10 11. The nucleic acid molecule of claim 10, comprising nucleotides 1657 to 3884 of SEQ ID NO: 1.

12. The nucleic acid molecule of claim 10, comprising nucleotides 1495 to 3884 of SEQ ID NO: 1.

15 13. The nucleic acid molecule of claim 10, comprising nucleotides 1 to 8253 of SEQ ID NO: 1.

14. A substantially pure polynucleotide encoding the Mcl-1s/ $\Delta$ TM amino acid sequence as set forth in SEQ ID NO: 3; or a polynucleotide complementary thereto.

20 15. The polynucleotide of claim 14, comprising nucleotides 1727 to 2414 of SEQ ID NO: 1 operatively linked to nucleotides 3768 to 3884 of SEQ ID NO: 1.

16. A vector comprising the polynucleotide of claim 14.

25 17. The vector of claim 16, which is an expression vector.

18. A host cell, which contains the vector of claim 16.

30 19. The polynucleotide of claim 14, which is a polyribonucleotide.

~~20.~~ A substantially pure oligonucleotide, comprising at least ten nucleotides that hybridize specifically to a nucleotide sequence of SEQ ID NO: 1 selected from the group consisting of:

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a nucleotide sequence comprising nucleotide position 2414 of SEQ ID NO: 1;

a nucleotide sequence comprising nucleotide position 2766 of SEQ ID NO: 1;

a nucleotide sequence comprising nucleotide position 3013 of SEQ ID NO: 1;

and

a nucleotide sequence comprising nucleotide position 3786 of SEQ ID NO: 1,

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wherein at least three nucleotides of said polynucleotide hybridize to a nucleotide sequence 5' and contiguous to said nucleotide position, and

wherein at least three nucleotides of said polynucleotide hybridize to a nucleotide sequence 3' and contiguous to said nucleotide position;

or an oligonucleotide complementary thereto.

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~~21.~~ A substantially pure oligonucleotide, comprising at least ten nucleotides that hybridize specifically to a nucleotide sequence of SEQ ID NO: 1 comprising nucleotides 2412 to 2414 of SEQ ID NO: 1 operatively linked to nucleotides 3768 to 3770 of SEQ ID NO: 1; or an oligonucleotide complementary thereto.

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~~22.~~ A substantially pure Mcl-1s/ $\Delta$ TM polypeptide, comprising an amino acid sequence as set forth in SEQ ID NO: 3, or a peptide portion thereof comprising at least three amino acids of the sequence set forth as amino acids 228 to 271 of SEQ ID NO: 3.

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23. A substantially pure antibody that interacts specifically with an epitope of the polypeptide of claim 22.

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24. A method of expressing a nucleic acid molecule in a cell, comprising introducing into the cell the Mcl-1 gene regulatory element of claim 1, whereby a nucleic acid molecule operatively linked to the Mcl-1 gene regulatory element is expressed in the cell.

25. The method of claim 24, whereby the Mcl-1 gene regulatory integrates into a region of genomic DNA in the cell, thereby operatively linking the Mcl-1 gene regulatory to an endogenous nucleic acid molecule, which is expressed from the Mcl-1 gene regulatory element.

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26. The method of claim 25, further comprising identifying the endogenous nucleic acid molecule.

27. The method of claim 24, whereby, prior to introducing the Mcl-1 gene regulatory element into the cell, the element is operatively linked to a heterologous nucleic acid molecule, wherein, following introduction into the cell, the heterologous nucleic acid molecule is expressed in the cell.

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28. The method of claim 24, wherein the cell is a hematopoietic cell.

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29. The method of claim 24, wherein the cell is involved in a pathologic condition.

30. The method of claim 29, wherein the cell is a leukemia cell.

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31. A method of identifying an agent that can modulate expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element, comprising the steps of:

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a) contacting under suitable conditions the Mcl-1 gene regulatory element of claim 1, at least a first protein that can interact specifically with the regulatory element, and an agent; and

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b) detecting a change in complex formation between the Mcl-1 gene regulatory element and the first protein, thereby identifying an agent that can modulate expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element.

32. The method of claim 31, wherein the first protein and the regulatory element interact specifically to form a complex in the absence of the agent.

33. The method of claim 31, wherein the agent alters a specific interaction of the first protein with the regulatory element.

34. The method of claim 33, wherein the agent disrupts the specific interaction of the first protein with the regulatory element, thereby identifying an agent that can decrease expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element.

35. The method of claim 33, wherein the agent induces an alteration of the first protein.

36. The method of claim 35, wherein the alteration is phosphorylation of the first protein, thereby identifying an agent that can increase the expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element.

37. The method of claim 31, wherein the first protein is selected from the group consisting of Sp1, serum response element binding factor (SRF), and Elk-1.

38. The method of claim 31, wherein the complex comprises Sp1, SRF, Elk-1, or a combination thereof.

39. The method of claim 31, wherein a second protein interacts specifically with a complex formed between the first protein and the regulatory element, whereby the agent alters a specific interaction of the second protein with the complex, thereby identifying an agent that can modulate expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element.

40. The method of claim 39, wherein the second protein is a kinase that can phosphorylate the first protein.

41. The method of claim 40, whereby the agent inhibits a specific interaction of the kinase with complex comprising the first protein, thereby identifying an agent that decreases expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element.

42. The method of claim 31, wherein, in the absence of the agent, the first protein does not bind specifically to the regulatory element, and wherein, in the presence of the agent, the first protein interacts specifically with the regulatory element to form a complex, thereby identifying an agent that can increase expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element.

43. The method of claim 31, further comprising contacting the first protein and the regulatory element with a compound that affects expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element.

44. The method of claim 43, wherein the compound inhibits expression of the nucleic acid molecule from the regulatory element.

45. The method of claim 44, wherein the compound is an ERK inhibitor.

46. The method of claim 44, wherein the agent alleviates inhibition of expression of the nucleic acid molecule from the regulatory element due to the compound, thereby identifying an agent that can increase expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element.

47. The method of claim 31, wherein suitable conditions are provided in a reaction mixture *in vitro*.

48. The method of claim 47, whereby the change in complex formation is identified using an electrophoretic mobility shift assay.

49. The method of claim 31, wherein suitable conditions are provided in a cell.

50. The method of claim 49, wherein the Mcl-1 gene regulatory element is operatively linked to a reporter nucleotide sequence, whereby the change in complex formation is identified by detecting a change in expression of the reporter nucleotide sequence.

51. The method of claim 31, wherein the agent is selected from the group consisting of a nucleotide sequence, a peptide, a peptidomimetic, and a small organic molecule.

52. A method of identifying an agent that can modulate expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element, comprising the steps of:

a) contacting under suitable conditions an agent and the Mcl-1 gene regulatory element of claim 1, which is operatively linked to a reporter nucleotide sequence; and

b) detecting an effect on expression of the reporter nucleotide sequence due to the agent, thereby identifying an agent that can modulate the expression of a nucleic acid molecule operatively linked to an Mcl-1 gene regulatory element.

53. The method of claim 52, wherein expression of the reporter nucleotide sequence is detected by detecting an RNA transcript of the reporter nucleotide sequence.

54. The method of claim 52, wherein expression of the reporter nucleotide sequence is detected by detecting a polypeptide encoded by the reporter nucleotide sequence.

55. The method of claim 54, wherein the polypeptide encoded by the reporter nucleotide sequence is detected by detecting an activity of the polypeptide selected from the group consisting of radioactivity, luminescence, chemiluminescence, fluorescence, enzymatic activity, and specific binding.

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56. The method of claim 52, wherein the reporter nucleotide sequence encodes a polypeptide selected from the group consisting of  $\beta$ -lactamase, chloramphenicol acetyltransferase, adenosine deaminase, aminoglycoside phosphotransferase, dihydrofolate reductase, hygromycin-B phosphotransferase, 10 thymidine kinase,  $\beta$ -galactosidase, and xanthine guanine phosphoribosyltransferase.

57. A method of inhibiting Mcl-1 gene expression in a cell, comprising introducing the Mcl-1 gene regulatory element of claim 1 into the cell.

15 58. The method of claim 57, whereby inhibiting Mcl-1 gene expression in the cell induces apoptosis of the cell.

59. The method of claim 57, whereby inhibiting Mcl-1 gene expression in the cell increases the viability of the cell.

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60. A method of modulating apoptosis in a cell, comprising introducing into the cell the nucleic acid molecule of claim 10.

25 61. The method of claim 60, wherein an Mcl-1 polypeptide encoded by exons 1, 2 and 3 is expressed from the nucleic acid molecule in the cell, thereby inhibiting apoptosis of the cell.

62. The method of claim 61, wherein the cell is a neuronal cell.

30 63. The method of claim 60, wherein an Mcl-1 $\Delta$ TM variant polypeptide encoded by exons 1 and 3 is expressed from the nucleic acid molecule in the cell, thereby inducing apoptosis of the cell.



64. The method of claim 63, wherein the cell is a tumor cell.

5 65. A method of inducing apoptosis of a cell, comprising expressing the Mcl-1s/ $\Delta$ TM polypeptide of claim 22 in the cell.

66. The method of claim 65, comprising introducing the polynucleotide of claim 14 into the cell, whereby the Mcl-1s/ $\Delta$ TM polypeptide is expressed in the cell.

10 67. The method of claim 65, wherein the cell is a tumor cell.

68. The method of claim 65, comprising introducing an oligonucleotide of claim 20 into the cell, wherein the oligonucleotide hybridizes specifically to a nucleotide sequence comprising a portion of an intron and a portion of exon 2, 15 whereby splicing of exon 2 is inhibited, and whereby the Mcl-1s/ $\Delta$ TM polypeptide is expressed in the cell.

69. A method of identifying a cellular factor that can be involved in splicing of an Mcl-1 gene transcript, comprising the steps of:

20 a) contacting in a reaction mixture a cellular extract and an oligonucleotide of claim 20; and

b) detecting a cellular factor that binds specifically to the oligonucleotide, thereby identifying a cellular factor that can be involved in splicing of the Mcl-1 gene transcript.

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70. The method of claim 69, wherein the cellular factor is involved in splicing exon 1 of the Mcl-1 gene transcript to exon 3 of the Mcl-1 gene transcript.

71. A method of identifying an agent that induces expression of the Mcl-1s/ $\Delta$ TM polypeptide of claim 22, comprising the steps of:

- 5           a) contacting a cell with the agent; and  
          b) detecting expression of the Mcl-1s/ $\Delta$ TM polypeptide or a  
ribonucleic acid molecule encoding the polypeptide, thereby identifying an  
agent that induces expression of the Mcl-1s/ $\Delta$ TM polypeptide.

72. A method of inducing apoptosis in a cell, comprising contacting the cell  
with the agent of claim 70.

10           73. A method of identifying a cell that expresses the Mcl-1s/ $\Delta$ TM  
polypeptide of claim 22, comprising contacting the cell with a reagent that interacts  
specifically with the Mcl-1s/ $\Delta$ TM polypeptide or with a ribonucleic acid molecule  
encoding the Mcl-1s/ $\Delta$ TM polypeptide.

15           74. The method of claim 73, wherein the reagent is the antibody of claim 23.

20           75. The method of claim 73, wherein the reagent is the oligonucleotide of  
claim 21.

25           76. A method of treating a subject having a pathologic condition, comprising  
affecting Mcl-1 expression in cells involved in the pathologic condition in the subject.

30           77. The method of claim 76, wherein the cells involved in the condition  
express an Mcl-1 gene product, said method comprising contacting the cells  
expressing the Mcl-1 gene product in the subject with an Mcl-1 gene regulatory  
element of claim 1, thereby reducing or inhibiting expression of the Mcl-1 gene  
product in the subject.

          78. The method of claim 76, comprising contacting the cells involved in the  
pathologic condition in the subject with the nucleic acid molecule of claim 10.

Method of claim 78,  
nucleic acid molecule  
biologic condition.

Method of claim 76,  
with the polynucleotide  
expressed in the cells,  
condition.

Method of claim 76,  
with the polynucleotide  
expressed in the cells,  
condition.

prising contact  
titude of claim 1  
by inducing a

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